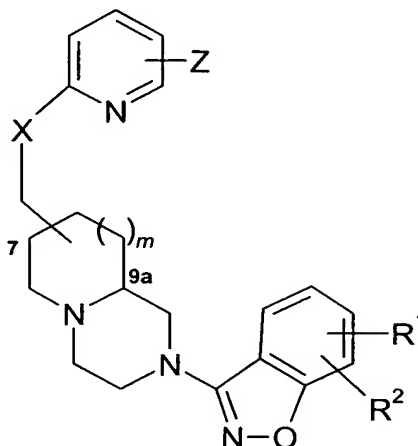
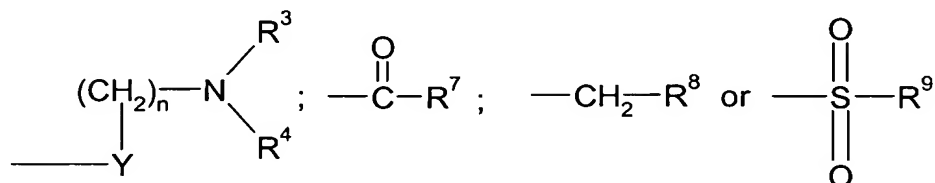


What is claimed is:

1. A compound having the formula



- 5 or the (R) or (S) enantiomer thereof, or the *cis* or *trans* isomer thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or of any of the foregoing, wherein m is 0 or 1; Z is



wherein R<sup>7</sup> is hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkoxy; R<sup>8</sup> is hydrogen, hydroxy, or (C<sub>1</sub>-C<sub>3</sub>)alkoxy; and R<sup>9</sup> is (C<sub>1</sub>-C<sub>3</sub>)alkoxy;

- 10 X is oxygen or NR, wherein R is hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl;

Y is methylene, wherein n is 0, 1 or 2; or oxygen, nitrogen or sulfur, wherein n is 2, 3 or 4;

- 15 R<sup>1</sup> and R<sup>2</sup> are each independently hydrogen, halogen, or a (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy or a (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkyl group, any one of which groups may be unsubstituted or substituted with one or more halogens;

R<sup>3</sup> and R<sup>4</sup> are each independently hydrogen, a (C<sub>1</sub>-C<sub>6</sub>)alkyl, a (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl, or a 5 to 6 membered heterocyclic group, any one of which groups may be unsubstituted or substituted with one or more of any of the following: (C<sub>1</sub>-C<sub>4</sub>)alkyl; (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>6</sub>-C<sub>10</sub>)aryl, a 5 to 6 member heterocyclic, amino, halogen or hydroxy groups; or

- 20 R<sup>3</sup> and R<sup>4</sup> together with the nitrogen atom to which they are attached form:

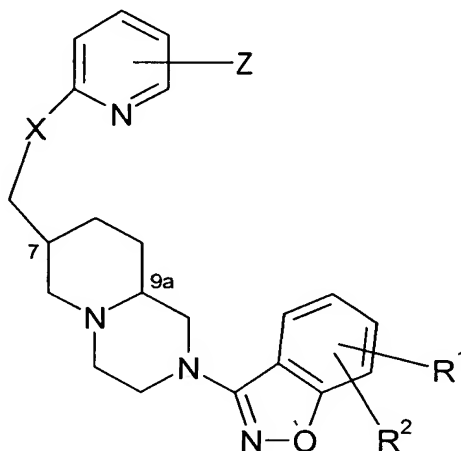
(i) a 3 to 7 membered optionally unsaturated monocyclic ring; or

EXPRESS MAIL  
EV 323 552 521 US

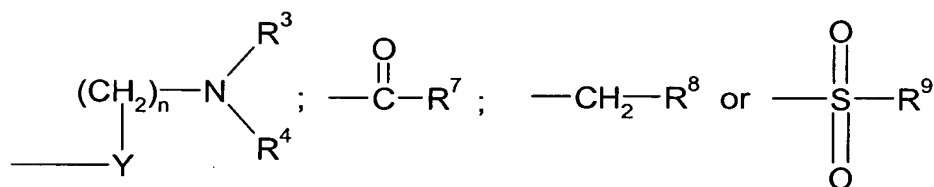
- (ii) a 4 to 10 membered optionally unsaturated polycyclic ring, wherein said monocyclic or polycyclic ring optionally has one or two additional heteroatoms selected from nitrogen, oxygen and sulfur,

wherein any of said rings (i) or (ii) may be unsubstituted or substituted with one or more (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>7</sub> to C<sub>13</sub>)aralkyl, a 5 to 10 membered heteroaryl, hydroxy, amino, cyano, or halogen groups.

2. The compound of Claim 1 having the structure:



wherein Z is



10

X is oxygen; n is 0; R<sup>1</sup> is hydrogen; R<sup>2</sup> is hydrogen or halogen; and R<sup>3</sup> is hydrogen or a (C<sub>1</sub>-C<sub>3</sub>)alkyl.

3. The compound of Claim 2 wherein R<sup>2</sup> is hydrogen; R<sup>3</sup> is hydrogen; and R<sup>4</sup> is

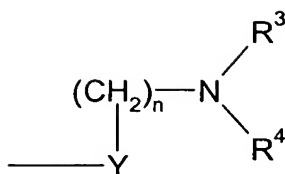
- a) a (C<sub>1</sub>-C<sub>6</sub>)alkyl group;  
 b) a (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl group; or  
 c) a 5 to 6 member heterocyclic group, wherein any one of which groups a), b) or c) may be unsubstituted or substituted with one or more of any of the following: (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, (C<sub>6</sub>-C<sub>10</sub>)aryl, a 5 to 6 member heterocyclic, amino, halogen or hydroxy groups.

20

4. The compound of Claim 3 wherein Z is

EXPRESS MAIL

EV 323 552 521 US

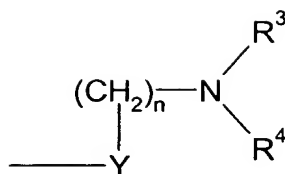


Y is methylene; and R<sup>4</sup> is

- a) a (C<sub>1</sub>-C<sub>4</sub>)alkyl which may be unsubstituted or substituted with one of the following: phenyl, cyclopropyl, methoxy, or substituted with a 5 to 6 membered heterocyclic, said heterocyclic having at least one nitrogen or oxygen atom;
- b) an unsubstituted (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl; or
- c) a 5 to 6 membered heterocyclic which can be unsubstituted or substituted with a (C<sub>1</sub>-C<sub>3</sub>)alkyl or a (C<sub>1</sub>-C<sub>3</sub>)alkoxy, said 5 to 6 member heterocyclic c) having at least one nitrogen atom and up to one other heteroatom selected from nitrogen, oxygen and sulfur.
5. The compound of Claim 4 wherein R<sup>4</sup> is
- a) an unsubstituted C<sub>4</sub> alkyl; a C<sub>3</sub> alkyl substituted with methoxy; a (C<sub>1</sub>-C<sub>2</sub>)alkyl substituted with phenyl or cyclopropyl; a (C<sub>1</sub>-C<sub>2</sub>)alkyl substituted with a 5 membered heterocyclic having a nitrogen or oxygen atom; or a (C<sub>1</sub>-C<sub>2</sub>)alkyl substituted with a 6 membered heterocyclic having at least one nitrogen;
- b) unsubstituted cyclopropyl; or
- c) a 5 to 6 membered ring which can be unsubstituted or substituted with a methyl or methoxy, said 5 to 6 membered ring c) having at least one nitrogen atom and up to one other heteroatom selected from nitrogen, oxygen and sulfur, said (C<sub>1</sub>-C<sub>3</sub>)alkyl is methyl and said (C<sub>1</sub>-C<sub>3</sub>)alkoxy is methoxy.
6. The compound of Claim 2 wherein R<sup>2</sup> is hydrogen; R<sup>3</sup> is (C<sub>1</sub>-C<sub>3</sub>)alkyl; and R<sup>4</sup> is
- a) a (C<sub>1</sub>-C<sub>4</sub>)alkyl group; or
- b) a (C<sub>5</sub>-C<sub>6</sub>)cycloalkyl group, either of which groups a) or b) may be unsubstituted or substituted with one or more (C<sub>1</sub>-C<sub>3</sub>)alkoxy or amino groups.
7. The compound of Claim 6 wherein said amino has the formula -NR<sup>5</sup>R<sup>6</sup> wherein R<sup>5</sup> and R<sup>6</sup> are each independently hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkyl.
8. The compound of Claim 7 wherein R<sup>4</sup> is
- a) a (C<sub>1</sub>-C<sub>4</sub>)alkyl group unsubstituted or substituted with one or more methoxy or amino groups wherein R<sup>5</sup> is hydrogen and R<sup>6</sup> is methyl; or
- b) an unsubstituted (C<sub>5</sub>-C<sub>6</sub>)cycloalkyl group.
9. The compound of Claim 1 wherein Z is

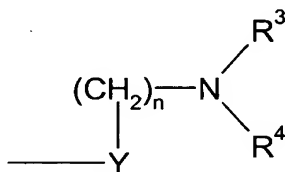
EXPRESS MAIL

EV 323 552 521 us



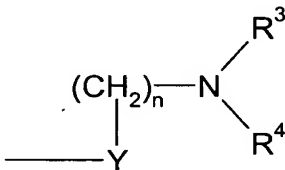
wherein Y is methylene; X is oxygen; n is 0; R<sup>1</sup> is hydrogen; R<sup>2</sup> is hydrogen; and R<sup>3</sup> and R<sup>4</sup> together with the nitrogen atom to which they are attached form i) a saturated non-aromatic 3 to 7 membered monocyclic ring, said ring i) being unsubstituted or substituted with one or more (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, or hydroxy groups.

10. The compound of Claim 1 wherein Z is



wherein Y is methylene; wherein X is oxygen; n is 0; R<sup>1</sup> is hydrogen; R<sup>2</sup> is hydrogen; and R<sup>3</sup> and R<sup>4</sup> together with the nitrogen atom to which they are attached form iii) an unsubstituted 5 to 6 membered heterocyclic ring, which heterocyclic ring, in addition to the nitrogen atom to which R<sup>3</sup> and R<sup>4</sup> are attached, has one additional nitrogen atom, or one sulfur or one oxygen atom.

11. The compound of Claim 2 wherein Z is



15 wherein Y is methylene; n is 0; R<sup>2</sup> is halogen; and R<sup>4</sup> is

a) a (C<sub>1</sub>-C<sub>5</sub>)alkyl;

b) a (C<sub>3</sub>-C<sub>6</sub>) cycloalkyl group, any of which groups a) or b) can be unsubstituted or substituted with one or more of any of the following: cyclopropyl; halogen; hydroxy; a 5 to 6 membered heterocyclic group wherein said 5 to 6 membered heterocyclic group may be unsubstituted or substituted with one or more methyl groups; or phenyl wherein said phenyl may be unsubstituted or substituted with one or more halogens; or R<sup>4</sup> is

c) a 5 member heterocyclic group.

12. The compound of Claim 11 wherein R<sup>2</sup> is fluorine; and R<sup>3</sup> is hydrogen or methyl.

13. The compound of Claim 2 wherein R<sup>2</sup> is halogen; and R<sup>3</sup> and R<sup>4</sup> together with the nitrogen atom to which they are attached form

EXPRESS MAIL  
EV 323 552 521 UKS

i) a saturated 3 to 7 membered monocyclic ring, which monocyclic ring may be unsubstituted or substituted with one or more phenyl, (C<sub>1</sub>-C<sub>3</sub>)alkyl, or (C<sub>1-4</sub>)alkoxy(C<sub>1-4</sub>)alkyl groups; or

ii) a 5 to 6 membered ring, which ring may be unsubstituted or substituted with one or more (C<sub>1</sub>-C<sub>3</sub>) alkyl groups, and which ring has one additional nitrogen or one oxygen atom.

14. The compound of Claim 1 wherein said compound is selected from the group consisting of:

(7R, 9aS)-trans-2-Benzo[d]isoxazol-3-yl-7-(6-morpholin-4-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-a]pyrazine;

7R, 9aS)-trans-2-Benzo[d]isoxazol-3-yl-7-(5-piperidin-1-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-a]pyrazine

7R, 9aS)-trans-2-(5-Fluoro-benzo[d]isoxazol-3-yl)-7-(5-pyrrolidin-1-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-a]pyrazine

(7R, 9aS)-trans-[6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-diethyl-amine

(7R, 9aS)-trans-[6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-dimethyl-amine

(7R, 9aS)-trans-[6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-ethyl-methyl-amine

(7R, 9aS)-trans-[6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(2-methoxy-1-methyl-ethyl)-amine

(7R, 9aS)-trans-[6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(2-methoxy-ethyl)-methyl-amine

(7R, 9aS)-trans-[6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-cyclopentyl-methyl-amine

(7R, 9aS)-trans-7-(5-Azetidin-1-ylmethyl-pyridin-2-yloxymethyl)-2-benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazine

(7R, 9aS)-trans-2-Benzo[d]isoxazol-3-yl-7-[5-(2-methyl-aziridin-1-ylmethyl)-pyridin-2-yloxymethyl]-octahydro-pyrido[1,2-a]pyrazine

(7R, 9aS)-trans-2-Benzo[d]isoxazol-3-yl-7-[5-(2-methoxymethyl-pyrrolidin-1-ylmethyl)-pyridin-2-yloxymethyl]-octahydro-pyrido[1,2-a]pyrazine

(7R, 9aS)-trans-[6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-tert-butyl-amine

(7S, 9aS)-cis-[6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-ethyl-methyl-amine

EXPRESS MAIL

EV 323552521 US

- (7S, 9aS)-cis-7-(5-Azetidin-1-ylmethyl-pyridin-2-yloxymethyl)-2-benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazine
- (7R, 9aS)-trans-[6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-dimethyl-amine
- 5 (7R, 9aS)-trans-Cyclohexyl-{6-[2-(5-fluoro-benzo[d]isoxazol-3-yl)-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-amine
- (7R, 9aS)-trans-2-(Ethyl-{6-[2-(5-fluoro-benzo[d]isoxazol-3-yl)-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-amino)-ethanol
- (7R, 9aS)-trans- 7-[6-(2,6-Dimethyl-piperidin-1-ylmethyl)-pyridin-2-yloxymethyl]-2-(5-fluoro-benzo[d]isoxazol-3-yl)-octahydro-pyrido[1,2-a]pyrazine
- 10 (7R, 9aS)-trans-(1,2-Dimethyl-propyl)-{6-[2-(5-fluoro-benzo[d]isoxazol-3-yl)-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-amine
- (7R, 9aS)-trans-[6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(2-methoxy-ethyl)-methyl-amine
- 15 (7R, 9aS)-trans-1-[6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(S)-pyrrolidin-3-ol
- (7R, 9aS)-trans-1-[6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-(R)-pyrrolidin-3-ol
- (7R, 9aS)-trans- 2-Benzo[d]isoxazol-3-yl-7-[5-(2-methyl-pyrrolidin-1-ylmethyl)-pyridin-2-yloxymethyl]-octahydro-pyrido[1,2-a]pyrazine
- 20 (7R, 9aS)-trans-1-[6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-piperidin-4-ol
- (7R, 9aS)-trans-Cyclopropyl-{6-[2-(5-fluoro-benzo[d]isoxazol-3-yl)-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-amine
- 25 (7R, 9aS)-trans-Cyclopropylmethyl-{6-[2-(5-fluoro-benzo[d]isoxazol-3-yl)-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-amine
- (7R, 9aS)-trans-2-(5-Fluoro-benzo[d]isoxazol-3-yl)-7-[6-(4-methyl-piperazin-1-ylmethyl)-pyridin-2-yloxymethyl]-octahydro-pyrido[1,2-a]pyrazine
- (7R, 9aS)-trans-2-(5-Fluoro-benzo[d]isoxazol-3-yl)-7-(6-piperidin-1-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-a]pyrazine
- 30 (7R, 9aS)-trans-{6-[2-(5-Fluoro-benzo[d]isoxazol-3-yl)-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-dimethyl-amine
- (7R, 9aS)-trans-{6-[2-(5-Fluoro-benzo[d]isoxazol-3-yl)-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-(tetrahydro-furan-2-ylmethyl)-amine
- 35 (7R, 9aS)-trans-7-[6-(2,5-Dimethyl-pyrrolidin-1-ylmethyl)-pyridin-2-yloxymethyl]-2-(5-fluoro-benzo[d]isoxazol-3-yl)-octahydro-pyrido[1,2-a]pyrazine

EXPRESS MAIL

Er 323 552521 us

(7R, 9aS)-trans-{6-[2-(5-Fluoro-benzo[d]isoxazol-3-yl)-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-[3-(4-methyl-piperazin-1-yl)-propyl]-amine

(7R, 9aS)-trans-{6-[2-(5-Fluoro-benzo[d]isoxazol-3-yl)-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl}-[3-(4-methyl-piperazin-1-yl)-propyl]-amine  
 5 benzo[d]isoxazol-3-yl)-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy]-pyrrolidin-1-yl-amine

7S, 9aS)-cis-[6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-3-ylmethyl]-cyclohexyl-methyl-amine

(7R, 9aS)-trans-1-[6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(S)-pyrrolidin-3-ol  
 10 (7R, 9aS)-trans-1-[6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-(R)-pyrrolidin-3-ol

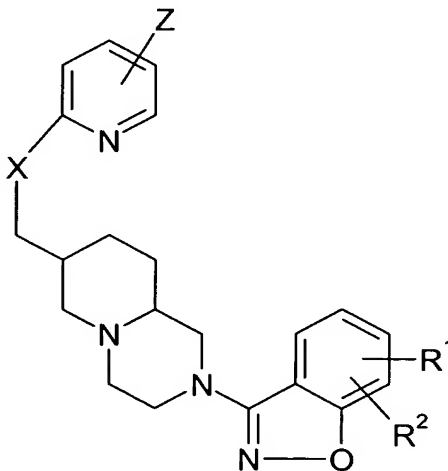
(7R, 9aS)-trans-2-Benzo[d]isoxazol-3-yl-7-(6-pyrrolidin-1-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-a]pyrazine

(7R, 9aS)-trans-[6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl]-benzyl-amine  
 15 ylmethoxy)-pyridin-2-ylmethyl]-benzyl-amine

7R, 9aS)-trans-2-Benzo[d]isoxazol-3-yl-7-(5-pyrrolidin-1-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-a]pyrazine; and

(7S, 9aS)-cis-2-Benzo[d]isoxazol-3-yl-7-(5-pyrrolidin-1-ylmethyl-pyridin-2-yloxymethyl)-octahydro-pyrido[1,2-a]pyrazine.

20 15. A compound of the formula:



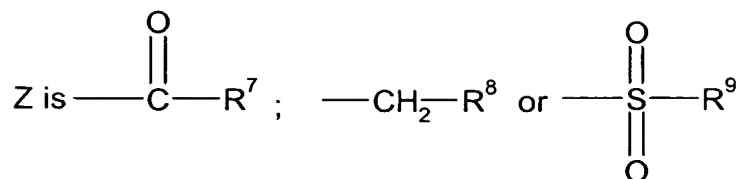
or an (R) or (S) enantiomer thereof, or the *cis* or *trans* isomer thereof,

wherein X is oxygen or NR, wherein R is hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl;

R<sup>1</sup> and R<sup>2</sup> are each independently hydrogen, halogen, or a (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy or a (C<sub>1</sub>-C<sub>6</sub>)alkoxy (C<sub>1</sub>-C<sub>6</sub>)alkyl group, any one of which groups may be  
 25 unsubstituted or substituted with one or more halogens; and

EXPRESS MAIL

EV 323 552521 445



wherein R<sup>7</sup> is hydrogen or (C<sub>1</sub>-C<sub>3</sub>)alkoxy; R<sup>8</sup> is hydrogen, hydroxy, or (C<sub>1</sub>-C<sub>3</sub>)alkoxy; and R<sup>9</sup> is (C<sub>1</sub>-C<sub>3</sub>)alkoxy.

16. The compound of Claim 15 wherein X is oxygen; R<sup>1</sup> is hydrogen; R<sup>2</sup> is hydrogen or fluorine; R<sup>7</sup> is methoxy; R<sup>8</sup> is hydroxy; and R<sup>9</sup> is methyl.

17. The compound of Claim 16 wherein said compound is selected from the group consisting of:

(7R, 9aS)-*trans*-6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-nicotinic acid methyl ester;

10 (7R, 9aS)-*trans*-6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-3-yl]-methanol.

(7R, 9aS)-*trans*-Methanesulfonic acid 6-(2-benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl ester;

15 (7R, 9aS)-*trans*-Methanesulfonic acid 6-[2-(5-fluoro-benzo[d]isoxazol-3-yl)-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy]-pyridin-2-ylmethyl ester;

(7R, 9aS)-*trans*-6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridine-2-carboxylic acid methyl ester;

(7R, 9aS)-*trans*-6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-2-yl]-methanol;

20 (7R, 9aS)-*trans*-{6-[2-(5-Fluoro-benzo[d]isoxazol-3-yl)-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy]-pyridin-2-yl}-methanol;

(7R, 9aS)-*trans*-6-[2-(5-Fluoro-benzo[d]isoxazol-3-yl)-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy]-pyridine-2-carboxylic acid ester;

25 (7R, 9aS)-*cis*-6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridine-2-carboxylic acid methyl ester;

7R, 9aS)-*cis*-6-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-2-yl]-methanol;

(7R, 9aS)-*cis*-Methanesulfonic acid 6-(2-benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl ester;

30 (7R, 9aS)-*trans*-5-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridine-2-carboxylic acid methyl ester;

(7R, 9aS)-*trans*-[5-(2-Benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-2-yl]-methanol; and

EXPRESS MAIL

EV 32355 25 21 45



(7R, 9aS)-*trans*-Methanesulfonic acid 5-(2-benzo[d]isoxazol-3-yl-octahydro-pyrido[1,2-a]pyrazin-7-ylmethoxy)-pyridin-2-ylmethyl ester.

18. A pharmaceutical composition comprising the compound of Claim 1 or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

5 19. A compound having binding activity for D2 and 5HT1B receptors wherein the ratio of D2 : 5HT1B inhibitory activity is about 20 or less.

20. The compound of Claim 29 wherein said compound is an aminomethylpyridinyloxymethyl/benzisoxazole.

10 21. A pharmaceutical composition comprising a therapeutically effective amount of the compound of Claim 19; and a pharmaceutically acceptable carrier.

22. A compound having effective binding activity to each of human D2, human 5HT1B and human 5HT2A receptors.

15 23. The compound of claim 22 wherein said effective binding activity comprises an in vivo effective  $K_i$  of no more than 20 nM at each of said D2 and 5HT2A receptors and no more than 5nM at the 5HT1B receptor.

24. A pharmaceutical composition comprising a therapeutically effective amount of the compound of Claim 23; and a pharmaceutically acceptable carrier.

20 25. A method for treating one or more central nervous system disorders comprising administering to a mammal in need of such treatment a therapeutically effective amount of the compound of Claim 1.

26. The method of Claim 25 wherein said one or more central nervous system disorders comprise schizophrenia and depression.

25 27. A method of treating one or more central nervous system disorders comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound which has at least 80% antagonism, or inverse agonist to each of D2, 5HT1B and 5HT2A receptors.

28. A method of treating one or more central nervous system disorders comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 19.

30 29. A method of treating one or more central nervous system disorders comprising administering to a mammal in need of such treatment a therapeutically effective amount of a D2, 5HT1B inhibitor having effective inhibitory activity with an in vivo effective  $K_i$  of no more than 15 nM at each of said receptors.

35 30. A method of treating a disorder selected from schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder; substance-induced psychotic disorder, personality disorder of the paranoid type, personality disorder of the

EXPRESS MAIL  
EV 32355 252145

schizoid type, panic disorder, phobias, obsessive-compulsive disorder, stress disorders, generalized anxiety disorder, movement disorders involving Huntington's disease, dyskinesia associated with dopamine agonist therapy, Parkinson's disease, restless leg syndrome, chemical dependencies, disorders comprising as a symptom thereof a deficiency in cognition, 5 dementias, mood disorders and episodes in a mammal; anxiety or psychotic disorders including schizophrenia, of the paranoid, disorganized, catatonic, undifferentiated, or residual type; schizophreniform disorder; schizoaffective disorder of the delusional type or the depressive type; delusional disorder; psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the 10 paranoid type; and personality disorder of the schizoid type, panic disorder; agoraphobia; a specific phobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; acute stress disorder; chemical dependencies: for alcohol, amphetamine, cocaine, opiate, nicotine addiction; disorders comprising, as a symptom thereof, a deficiency in cognition, a subnormal functioning in one or more cognitive aspects; deficiency in memory, intellect, or 15 learning and logic ability, in a particular individual relative to other individuals within the same general age population; reduction in any particular individual's functioning in one or more cognitive aspects, age-related cognitive decline; dementia, Alzheimer's disease, multi-infarct dementia, alcoholic dementia or other drug-related dementia, dementia associated with intracranial tumors or cerebral trauma, dementia associated with Huntington's disease or 20 Parkinson's disease, or AIDS-related dementia; Alzheimer's related dementia; delirium; amnesic disorder; post-traumatic stress disorder; mental retardation; a learning disorder, for example reading disorder, mathematics disorder, or a disorder of written expression; attention-deficit/hyperactivity disorder; and age-related cognitive decline; mood disorders or mood episodes; major depressive episode of the mild, moderate or severe type, a manic or 25 mixed mood episode, a hypomanic mood episode; a depressive episode with atypical features; a depressive episode with melancholic features; a depressive episode with catatonic features; a mood episode with postpartum onset; post-stroke depression; major depressive disorder; dysthymic disorder; minor depressive disorder; premenstrual dysphoric disorder; post-psychotic depressive disorder of schizophrenia; a major depressive disorder 30 superimposed on a psychotic disorder; delusional disorder or schizophrenia; a bipolar disorder, bipolar I disorder, bipolar II disorder, and cyclothymic disorder, disorders subject to treatment by inhibition of any or all of the D2, 5HT1B, and 5HT2A receptors: hypertension, depression; depression in cancer patients, depression in Parkinson's patients, postmyocardial infarction depression, subsyndromal symptomatic depression, depression in infertile women, 35 pediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, and post partum depression, generalized anxiety disorder,

EXPRESS MAIL

EV 323 552 521 US

phobias; agoraphobia, social phobia and simple phobias, posttraumatic stress syndrome, avoidant personality disorder, premature ejaculation, eating disorders; anorexia nervosa and bulimia nervosa, obesity, chemical dependencies, addictions to alcohol, cocaine, heroin, phenobarbital, nicotine and benzodiazepines, cluster headache, migraine, pain, Alzheimer's disease, obsessive-compulsive disorder, panic disorder, memory disorders; dementia, amnestic disorders, and age-related cognitive decline (ARCD), Parkinson's diseases; dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias, endocrine disorders; hyperprolactinaemia, vasospasm, vasospasm in the cerebral vasculature, cerebellar ataxia, gastrointestinal tract disorders involving changes in motility and secretion, negative symptoms of schizophrenia, schizoaffective disorder, obsessive compulsive disorder, mania, premenstrual syndrome, fibromyalgia syndrome, stress incontinence, Tourette's syndrome, trichotillomania, kleptomania, male impotence, cancer; small cell lung carcinoma, chronic paroxysmal hemicrania and headache associated with vascular disorders. comprising administering to a mammal in need of such treatment a therapeutically effective amount of the compound of Claim 1.

31. A method of treating a disorder selected from schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder; substance-induced psychotic disorder, personality disorder of the paranoid type, personality disorder of the schizoid type, panic disorder, phobias, obsessive-compulsive disorder, stress disorders, generalized anxiety disorder, movement disorders involving Huntington's disease, dyskinesia associated with dopamine agonist therapy, Parkinson's disease, restless leg syndrome, chemical dependencies, disorders comprising as a symptom thereof a deficiency in cognition, dementias, mood disorders and episodes in a mammal; anxiety or psychotic disorders including schizophrenia, of the paranoid, disorganized, catatonic, undifferentiated, or residual type; schizophreniform disorder; schizoaffective disorder of the delusional type or the depressive type; delusional disorder; psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; and personality disorder of the schizoid type, panic disorder; agoraphobia; a specific phobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; acute stress disorder; chemical dependencies: for alcohol, amphetamine, cocaine, opiate, nicotine addiction; disorders comprising, as a symptom thereof, a deficiency in cognition, a subnormal functioning in one or more cognitive aspects; deficiency in memory, intellect, or learning and logic ability, in a particular individual relative to other individuals within the same general age population; reduction in any particular individual's functioning in one or more cognitive aspects, age-related cognitive decline; dementia, Alzheimer's disease, multi-infarct dementia, alcoholic dementia or other drug-related dementia, dementia associated with

EXPRESS MAIL

EV 323 552 521 U.S.

intracranial tumors or cerebral trauma, dementia associated with Huntington's disease or Parkinson's disease, or AIDS-related dementia; Alzheimer's related dementia; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a learning disorder, for example reading disorder, mathematics disorder, or a disorder of written expression; 5 attention-deficit/hyperactivity disorder; and age-related cognitive decline; mood disorders or mood episodes; major depressive episode of the mild, moderate or severe type, a manic or mixed mood episode, a hypomanic mood episode; a depressive episode with atypical features; a depressive episode with melancholic features; a depressive episode with catatonic features; a mood episode with postpartum onset; post-stroke depression; major depressive 10 disorder; dysthymic disorder; minor depressive disorder; premenstrual dysphoric disorder; post-psychotic depressive disorder of schizophrenia; a major depressive disorder superimposed on a psychotic disorder; delusional disorder or schizophrenia; a bipolar disorder, bipolar I disorder, bipolar II disorder, and cyclothymic disorder, disorders subject to treatment by inhibition of any or all of the D2, 5HT1B, and 5HT2A receptors: hypertension, 15 depression; depression in cancer patients, depression in Parkinson's patients, postmyocardial infarction depression, subsyndromal symptomatic depression, depression in infertile women, pediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, and post partum depression, treatment resistant depression, SSRI-resistant depression, autism, post operative cognitive decline, generalized anxiety 20 disorder, phobias; agoraphobia, social phobia and simple phobias, posttraumatic stress syndrome, avoidant personality disorder, premature ejaculation, eating disorders; anorexia nervosa and bulimia nervosa, obesity, chemical dependencies, addictions to alcohol, cocaine, heroin, phenobarbital, nicotine and benzodiazepines, cluster headache, migraine, pain, Alzheimer's disease, obsessive-compulsive disorder, panic disorder, memory disorders; 25 dementia, amnestic disorders, and age-related cognitive decline (ARCD), Parkinson's diseases; dementia in Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias, treatment resistant depression, SSR1 failures, autism, post operative cognitive decline, endocrine disorders; hyperprolactinaemia, vasospasm, vasospasm in the cerebral vasculature, cerebellar ataxia, gastrointestinal tract disorders involving changes in motility and 30 secretion, negative symptoms of schizophrenia, schizoaffective disorder, obsessive compulsive disorder, mania, premenstrual syndrome, fibromyalgia syndrome, stress incontinence, Tourette's syndrome, trichotillomania, kleptomania, male impotence, cancer; small cell lung carcinoma, chronic paroxysmal hemicrania and headache associated with vascular disorders. comprising administering to a mammal in need of such treatment a 35 therapeutically effective amount of the compound of Claim 22.

EV 3 23 55 25 21 45  
EXPRESS MAIL